

1. (Amended) A method for preparing a nucleic acid binding protein that binds to a target nucleotide sequence, wherein the binding protein comprises a plurality of zinc fingers of the Cys2-His2 class, wherein the method comprises:

- i) selecting a quadruplet within the target nucleotide sequence;
- ii) designing the binding protein such that binding of a zinc finger to the quadruplet is obtained by choosing the sequence of particular residues of the zinc finger depending on the nucleotide sequence of the quadruplet, as follows:
 - a) if base 4 in the quadruplet is A, then position +6 in the α -helix is Glu, Asn or Val;
 - b) if base 4 in the quadruplet is C, then position +6 in the α -helix is Ser, Thr, Val, Ala, Glu or Asn
 - iii) synthesizing a polynucleotide encoding the binding protein of (ii);
 - iv) introducing the polynucleotide of (iii) into a cell; and
 - v) incubating the cell under conditions in which the encoded nucleic acid binding protein is expressed.

Please amend claim 2 as follows:

2. (Amended) A method according to claim 1, wherein binding to base 4 of the quadruplet by a zinc finger is additionally determined as follows:

- c) if base 4 in the quadruplet is G, then position +6 in the α -helix is Arg or Lys;
- d) if base 4 in the quadruplet is T, then position +6 in the α -helix is Ser, Thr, Val or Lys.

Please amend claim 3 as follows:

3. (Amended) A method for preparing a nucleic acid binding protein that binds to a target nucleotide sequence, wherein the binding protein comprises a plurality of zinc fingers of the Cys2-His2 class, wherein the method comprises:

- i) selecting a quadruplet within the target nucleotide sequence;
- ii) designing the binding protein such that binding of a zinc finger to the quadruplet is obtained by choosing the sequence of particular residues of the zinc finger depending on the nucleotide sequence of the quadruplet, as follows:
 - a) if base 4 in the quadruplet is G, then position +6 in the α -helix is Arg or Lys;
 - b) if base 4 in the quadruplet is A, then position +6 in the α -helix is Glu, Asn or Val;
 - c) if base 4 in the quadruplet is T, then position +6 in the α -helix is Ser, Thr, Val or Lys;
 - d) if base 4 in the quadruplet is C, then position +6 in the α -helix is Ser, Thr, Val, Ala, Glu or Asn;
 - e) if base 3 in the quadruplet is G, then position +3 in the α -helix is His;
 - f) if base 3 in the quadruplet is A, then position +3 in the α -helix is Asn;
 - g) if base 3 in the quadruplet is T, then position +3 in the α -helix is Ala, Ser or Val; provided that if it is Ala, then one of the residues at -1 or +6 is a small residue;
 - h) if base 3 in the quadruplet is C, then position +3 in the α -helix is Ser, Asp, Glu, Leu, Thr or Val;
 - i) if base 2 in the quadruplet is G, then position -1 in the α -helix is Arg;
 - j) if base 2 in the quadruplet is A, then position -1 in the α -helix is Gln;

AS
Concluded

- k) if base 2 in the quadruplet is T, then position -1 in the α -helix is His or Thr;
- l) if base 2 in the quadruplet is C, then position -1 in the α -helix is Asp or His;
- m) if base 1 in the quadruplet is G, then position +2 is Glu;
- n) if base 1 in the quadruplet is A, then position +2 Arg or Gln;
- o) if base 1 in the quadruplet is C, then position +2 is Asn, Gln, Ara, His or Lys;
- p) if base 1 in the quadruplet is T, then position +2 is Ser or Thr

iii) synthesizing a polynucleotide encoding the binding protein of (ii);
iv) introducing the polynucleotide of (iii) into a cell; and
v) incubating the cell under conditions in which the encoded nucleic acid binding protein is expressed.

ED
ACJ

Please amend claim 4 as follows:

4. (Amended) A method according to any preceding claim, wherein the each zinc finger has the general primary structure

X^a Cys X_{2-4} Cys- X_{2-3} -Rhe- X^c -X-X-X-X-Leu-X-X-His-X-X- X^b His-linker (SEQ ID NO: 3)

1 1 2 3 4 5 6 7 8 9

wherein X (including X^a , X^b and X^c) is any amino acid.

Claim 5 was amended as follows:

5. (Twice Amended) A method according to claim 4 wherein Xa is Phe/Tyr-X or Pro-Phe/Tyr-X.

Please amend claim 6 as follows:

6. (Twice Amended) A method according to claim 5 wherein X_{2-4} is selected from any one of:

Ser-X, Glu-X, Lys-X, Thr-X, Pro-X and Arg-X.

Please amend claim 7 as follows:

7. (Twice Amended) A method according to claim 4 wherein X^b is Thr or Ile.

Please amend claim 8 as follows:

8. (Twice Amended) A method according to claim 4 wherein X^{2-4} is Gly-Lys-Ala, Gly-Lys-Cys, Gly-Lys-Ser, Gly-Lys-Gly, Met-Arg-Asn or Met-Arg.

Please amend claim 9 as follows:

9. (Twice Amended) A method according to claim 4 wherein the linker is Thr-Gly-Glu-Lys (SEQ ID NO: 4) or Thr-Gly-Glu-Lys-Pro (SEQ ID NO: 5).

Please amend claim 10 as follows:

10. (Twice Amended) A method according to claim 4 wherein position +9 is Arg or Lys.

Please amend claim 11 as follows:

11. (Twice Amended) A method according to claim 4 wherein positions +1, +5 and +8 are not occupied by any one of the hydrophobic amino acids, Phe, Trp or Tyr.

Please amend claim 12 as follows:

12. (Amended) A method according to claim 11 wherein positions +1, +5 and +8 are occupied by the residues Lys, Thr and Gln respectively.

Please amend claim 13 as follows:

13. (Amended) A method for preparing a nucleic acid binding protein of the Cys2-His2 zinc finger class which binds a target nucleic acid sequence, comprising the steps of:

This claim is not canceled

- a) selecting a model zinc finger domain from the group consisting of naturally occurring zinc fingers and consensus zinc fingers; and
- b) mutating the finger according to the rules set in any one of claims 1 to 3.

Please amend claim 14 as follows:

14. (Twice Amended) A method according to claim 13, wherein the model zinc finger is a consensus zinc finger whose structure is selected from the group consisting of the consensus structure Pro-Tyr-Lys-Cys-Pro-Glu-Cys-Gly-Lys-Ser-Phe-Ser-Gln-Lys-Ser-Asp-Leu-Val-Lys-His-Gln-Arg-Thr-His-Thr-Gly (SEQ ID NO: 6), and the consensus structure Pro-Tyr-Lys-Cys-Ser-Glu-Cys-Gly-Lys-Ala-Phe-Ser-Gln-Lys-Ser-Asn; Leu-Thr-Arg-His-Gln-Arg-Ile-His-Thr-Gly-Glu-Lys-Pro (SEQ ID NO: 7).

Please amend claim 15 as follows:

15. (Amended) A method according to claim 13 wherein the model zinc finger is a naturally-occurring zinc finger whose structure is selected from one finger of a protein selected from the group consisting of Zif 268 [(Elrod-Erickson *et al.*, (1996) Structure 4:1171-1180)], GLI, Tramtrack and YY1.

Please amend claim 18 as follows:

18. (Twice Amended) A method according to claim 14, wherein the N-terminal zinc finger is preceded by a leader peptide having the sequence Met-Ala-Glu-Glu-Lys-Pro (SEQ ID NO: 8).

Please amend claim 19 as follows:

19. (Twice Amended) A method according to claim 13 wherein the nucleic acid binding protein is obtained by recombinant nucleic acid technology, the method comprising the steps of:

- a) preparing a nucleic acid coding sequence encoding two or more model zinc finger domains, placed N-terminus to C-terminus;
- b) inserting the nucleic acid sequence into a suitable expression vector; and
- c) expressing the nucleic acid sequence in a host organism in order to obtain the nucleic acid binding protein.

Claim 22 was amended as follows:

22. A method according to claim 21, comprising the steps of:

- a) preparing a nucleic acid construct which express a fusion protein comprising the nucleic acid binding protein and a minor coat protein of a filamentous bacteriophage;
- b) preparing further nucleic acid constructs which express a fusion protein comprising a selectively mutated nucleic acid binding protein and a minor coat protein of a filamentous bacteriophage;
- c) causing the fusion proteins defined in steps (a) and (b) to be expressed on the surface of bacteriophage transformed with the nucleic acid constructs;